CLINICAL ONCOLOGY ALERT
Providing Evidence-based Clinical Information for 18 Years
A monthly update of developments in cancer treatment and research
Thomson American Health Consultants Home Page—http://www.ahcpub.com
CME for Physicians—http://www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Practicability and Acute Hematological Toxicity of 2- and 3-Weekly CHOP and CHOEP Chemotherapy for Aggressive Non-Hodgkin's Lymphoma

ABSTRACT & COMMENTARY

Synopsis: Since the introduction of the 3-weekly CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy 25 years ago, many efforts have been undertaken to improve the efficacy of multicycle polychemotherapy for patients with aggressive lymphoma. A variety of regimens were invented by adding drugs and alternating schedules. In a prospective, randomized trial, the current every 3-week CHOP regimen was considered the standard chemotherapy regimen for aggressive lymphoma.[1] This study was done in the era prior to the widespread use of hematopoietic growth factors. Studies with growth factors to increase dose intensity were not successful enough to alter the standard of care.[2] In older patients, CHOP variants have also been published but have yet to yield improvement in overall outcome.[3] The addition of rituximab to this standard has recently been shown to improve outcome in older patients.[4] The German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) investigated whether specific intensifications of the classical 3-weekly CHOP regimen could improve overall outcome. One was the addition of another cytotoxic agent. Etoposide was chosen due to data showing efficacy in lymphoma. The second method was the shortening of the time intervals of the CHOP regimen. This was done with the use of G-CSF (filgrastim).

Source: Wunderlich A, et al. *Ann Oncol.* 2003;14:881-893.

In 1993 the dshnhl activated a multicenter, randomized phase III trial called NHL-B. Four treatment options were compared in a 2 × 2 factorial design. CHOP chemotherapy was planned to be given in 21-day intervals without rhG-CSF (CHOP-21) or in 14-day intervals with the addition of rhG-CSF (CHOP-14). Two further treatment arms resulted from the addition of etoposide (CHOEP-21 and CHOEP-14). The trial was formally split into 2 trials as 2 different groups of patients were enrolled. One trial (NHL-

Volume 18 • Number 8 • August 2003 • Pages 57-64

B1) included patients younger than 60 years of age with a low-risk profile lactate dehydrogenase [LDH] below the upper normal value). The second trial (NHL-B2) included patients between 61 and 75 years of age irrespective of the risk profile. Patients younger than 60 years of age with an elevated LDH value were included in a different trial of the study group (NHL-A), comparing conventional CHOEP-21 with a strategy including high-dose chemotherapy and autologous bone marrow transplantation. Wunderlich and colleagues have recently shown that CHOP-14 has improved outcome in older patients and that CHOEP-14 is superior in younger patients or those with low-risk disease.[5,6]

COMMENT BY STUART M. LICHTMAN, MD, FACP

This paper analyzes the practicality of the 4 CHOP variants by analyzing how well the intended schedules could be applied, to what extent dose erosion occurred, and what spectrum of dose-limiting toxicities occurred. The study analyses 959 patients, with slightly less than half (456 patients) being older than 60 years of age. The oldest patient in the study was 75 years. Chemotherapy regimens that were administered were G-CSF only in the 2-week regimens and were given for 10 days. The dose adherence in the NHL-B1 trial was excellent. The median relative dose actually given compared to planned dose exceeded 98% for the myelosuppressive drugs in all 4 regimens. Addition of etoposide, however, was accompanied by more dose erosion. CHOP-14 and CHOP-21 were similar regarding toxicity profile, rate of infection, use of antibiotics, rate of transfusions, and hospitalization. CHOEP schemes were associated with a higher rate of infections, more transfusion requirements, more antibiotic use, and longer hospitalization than the CHOP schemes, particularly in patients older than 60 years. Hematopoietic recovery was age- and treatment-related. The addition of etoposide is feasible and safe for patients up to 60 years old in both the CHOEP-21 and CHOEP-14 schemes. For patients older than 60 years of age, the addition of etoposide is associated with marked dose erosion due to increased toxicity. In this age group CHOEP should be used with caution. Wunderlich et al attempted to lower the duration of G-CSF to 7 days (RICOVER-60).[7] CHOP-14 could be recycled as timely in RICOVER-60 as in NHL-B2. However, the rate of CHOP-14 cycles with WHO grade-3 and grade-4 infections doubled from 2.4% in the NHL-B2 trial to 5.2% in the RICOVER trial. Similarly, the cycles with the use of intravenous antibiotics rose from 15.2% to 20.8%. While reduced G-CSF application does not affect the feasibility of the biweekly CHOP-14 regimen in elderly patients with aggressive lymphoma, it increases infection rates considerably. They recommend a 10-day schedule of G-CSF starting on day 4 and caution against the substitution of filgrastim by PEG-filgrastim in the CHOP-14 regimen.

Therefore, these studies indicate that a change in the standard of care of aggressive lymphoma may be appropriate. A 14-day regimen of CHOP may improve outcome in older patients and CHOEP in younger patients. G-CSF must be used in the 14-day regimens in a 10-day schedule. Since the 14-day schedule did not include patients older than 75 or those with significant comorbidity, extrapolation of the results to these groups may be made with caution. The addition of rituximab to these regimens must be further explored. ■

References

1. Fisher RI, et al. *N Engl J Med*. 1993;328:1002-1006.
2. Shipp MA, et al. *J Clin Oncol*. 1995;13:2916-2923.
3. Lichtman SM. *Crit Rev Oncol Hematol*. 2000;33: 119-128.
4. Coiffier B, et al. *N Engl J Med*. 2002;346:235-242.
5. Pfreundschuh M, et al. *Blood*. 2002;99 (suppl 1):340a.

Clinical Oncology Alert, ISSN 0886-7186, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina.

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Clinical Oncology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information
Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@ahcpub.com
Editorial E-Mail Address:
robert.kimball@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices
United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $145).
Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191 each.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation
Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.
AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments
Please call Robin Mason, Managing Editor, at (404) 262-5517 or Robert Kimball, Assistant Managing Editor, at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Ershler is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Dr. Albertini does research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals. Drs. Hawkins, Kaplan, Kotz, and Morris report no relationships related to this field of study. Drs. Canellos, Chabner, Einhorn, Goodman, Lippman, Pinedo, and Sutton did not return financial disclosures.

6. Pfreundschuh M, et al. *Blood*. 2002;99 (suppl 1):3060a.
7. Kloess M, et al. *Proc Annu Meet Am Soc Clin Oncol.* 2003;22:2402a.

Platinum-Paclitaxel As Second-Line Chemotherapy for Relapsed Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: There has been some controversy on the role of taxanes in combination with platinum for the treatment of ovarian cancer. In the current report, patients who relapsed after a disease-free interval of 6 months or more were randomized in 2 large, multicenter trials conducted in Europe to receive either platinum (or typical platinum-based regimens) or paclitaxel plus platinum. Analysis of the data after a median follow-up of 42 months demonstrated progression-free and overall survival advantage for those receiving platinum with paclitaxel. Although complexities in the study design make conclusions far from absolute, the data presented make a strong case for paclitaxel in this setting.

Source: The ICON and AGO Collaborators. *Lancet.* 2003;361:2099-2106.

Despite improvements in first-line chemotherapy for ovarian cancer, most patients recur within 3 years of diagnosis.[1] The choice of second-line chemotherapy remains controversial, and it is apparent that the success of second-line therapy depends, to a large extent, on the disease-free interval (DFI) after initial chemotherapy. The standard of care recently has been to tailor chemotherapy based upon whether the DFI was greater than 6 months. Platinum-based chemotherapy is most frequently given when the DFI is 6 months or greater, but alternative agents are often chosen if the interval had been less than 6 months. The current report represented a joint effort from the International Collaborative Ovarian Neoplasm 4 (ICON 4) and Arbeitsgemeinschaft Gynaekologische Onkologie (AGO), both of which conducted multicenter, randomized trials for patients who had recurrent ovarian cancer and were considered platinum-sensitive on the basis of a greater than 6 month DFI after initial chemotherapy. All patients received platinum chemotherapy initially, and some had also received paclitaxel as part of the first-time treatment. The ICON 4 and AGO trials were run parallel to each other. Enrolled in this study were 802 patients from 119 different hospitals throughout Europe. Eligible patients had relapsed epithelial ovarian cancer requiring chemotherapy; previously received platinum-based chemotherapy; and were treatment free for greater than 6 months (AGO) or 12 months (ICON 4).

The patients were randomly assigned to either conventional platinum-based therapy or platinum and paclitaxel. Chemotherapy was administered every 3 weeks. The dose of carboplatin was determined by the area under the curve (AUC) method of Calvert and was a minimum of 5. Patients who enrolled through ICON 4 received either carboplatin or cisplatin. The carboplatin was set at a dose of AUC 5, whereas the cisplatin was given at a minimum dose of 75 mg/m^2 (if given as a single agent) or 50 mg/m^2 (if given in combination with other drugs). Patients in ICON 4 assigned paclitaxel plus platinum chemotherapy were to receive 175 mg/m^2 of paclitaxel given in a 3-hour infusion, followed by either the carboplatin or cisplatin at the dose mentioned above. Patients in the AGO protocol assigned paclitaxel plus carboplatin received 185 mg/m^2 of paclitaxel given in a 3-hour infusion, followed by carboplatin as noted above. Analysis was by intention to treat.

After a median follow-up of 42 months, 530 patients had died. The survival curves revealed a difference in favor of paclitaxel plus platinum (hazard ratio, 0.82; 95% CI, 0.69-0.97; P = .02). This corresponded to an absolute difference in 2-year survival of 7% between the group receiving paclitaxel and that receiving platinum without paclitaxel (57 vs 50%; 95% CI for a difference, 1%-12%), and median survival of 5 months (29 vs 24 months; CI for a difference, 1 month-11 months). Of the 820 patients randomized, 717 developed progressive disease or died. The progression-free survival curves showed a difference in favor of paclitaxel plus platinum (hazard ratio, 0.76; [0.66-0.89], P = .0004), corresponding to an absolute difference in 1-year progression-free survival of 10% (50 vs 40% [4-15]) and in median progression survival of 3 months (13 vs 10 months [1-5]). Thus, the paclitaxel plus platinum chemotherapy was noted to improve survival and progression-free survival among patients with relapsed, platinum-sensitive ovarian cancer.

COMMENT BY WILLIAM B. ERSHLER, MD

The findings from this analysis were presented at the ASCO meeting this year and generated a lively discussion, particularly in light of prior data published from ICON indicating no advantage to using paclitaxel with carboplatin as initial therapy for ovarian cancer.[2] The prior ICON study, which had demonstrated no added

benefit of paclitaxel, runs counter to the common impression of the superiority of taxane-platinum combinations in the initial therapy for ovarian cancer, and some interpreted the current finding as an endorsement of the importance of paclitaxel in the treatment of this disease. The presenters at ASCO, in defense of the prior ICON findings, speculated that patients with recurrent disease were less capable of receiving full-dose platinum, and thus benefited from the added taxane. They pointed out that in the current trial only 40% of patients received 90% or more of the planned dose of carboplatin.

Another finding from this study that was quite important and perhaps unexpected was that the combination of paclitaxel plus platinum resulted in no added impairment in quality of life, including measures of global health status, fatigue, nausea, vomiting, and pain. Thus, the study had demonstrated added benefit from paclitaxel in combination with platinum chemotherapy in terms of both survival and progression-free survival in those with relapsed ovarian cancer and a DFI of 6 months or more.

As pointed out in the accompanying editorial,[3] a number of questions remain. In that editorial, Kaye points out that the extent of benefit in certain subgroups was only modest, and before a global recommendation can be fully endorsed (and established as standard of care), additional, confirmatory studies would be indicated. For example, women who relapsed between 6 and 12 months after initial therapy had only modest demonstrable benefit compared to those with a DFI of greater than 12 months. Similarly, those who had received paclitaxel as initial therapy had less convincing demonstrable benefit with paclitaxel as salvage therapy.

Although the data give some guidance with regard to optimal management, the use of a chemotherapy strategy that was not curative initially defines the scope of expectations in terms of quality of life and added months of survival. However, the need to develop new, more effective agents and combinations should remain the primary goal for the overall advancement of care for ovarian cancer. Short of the appearance of effective new agents and approaches, the reapplication of drugs that produced a DFI of a year or so can, at best, be expected to do the same again, and this falls far short of the ultimate goal of cure. ■

References

1. Parkin DM, et al. *Eur J Cancer*. 2001;37:S4-S66.
2. ICON Collaborators. *Lancet*. 2002;360:505-515.
3. Kaye SB. *Lancet*. 2003;361:2094-2095.

Reduced Cardiac Risk for Breast Cancer Survivors

ABSTRACT & COMMENTARY

Synopsis: Women who survive breast cancer may be at a lower risk of developing coronary artery disease compared with women without a history of breast cancer. In this population-level cohort study, Lamont and colleagues from the University of Chicago analyzed data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Medicare program to study the cardiac risk of elderly female Medicare beneficiaries with or without a history of breast cancer. They found that the risk for hospitalization for acute myocardial infarction was reduced significantly (34%) among the breast cancer survivors. Lamont et al speculate that, among other possibilities, the protective effect of prior breast cancer upon the development of acute myocardial infarction may be due to the use of selective estrogen response modifiers (SERMS) for the treatment of the breast cancer.

Source: Lamont EB, et al. *Cancer*. 2003;98:2-10.

Estrogen is strongly associated with both health and disease in women. Comparatively high estrogen exposure is protective against some diseases (eg, coronary heart disease and osteoporosis) but contributory to others (eg, breast and endometrial carcinoma). Recently, Lamont and associates from the University of Chicago have demonstrated that breast cancer survivors have reduced rates of osteoporosis (*this manuscript is currently in press*). In the current report, an examination of coronary artery disease as manifest by acute myocardial infarction was undertaken in postmenopausal women who have survived breast cancer. The report details an investigation of the National Cancer Institutes Surveillance, Epidemiology and End Results (SEER) Medicare Program. Elderly women survivors of stage 0, I, or II breast carcinoma (n = 5980) diagnosed between the ages of 55 and 64 were compared with age-matched women without a history of cancer (n = 23165) derived using the Medicare 5% Noncancer File. In addition to age, Lamont et al controlled the analyses for race, socioeconomic status, geographic location, cohort entry year, and medical comorbidity.

The hazard of hospitalization for acute myocardial infarction (AMI) for breast cancer survivors relative to the comparison group was 0.66 (95% CI, 0.49-0.88).

The apparent cardioprotective effect was stronger in breast cancer survivors with documented cardiac risk factors. Lamont et al conclude that survivors of early stage, postmenopausal breast cancer are at significantly lower risk of hospitalization for acute myocardial infarction than women who do not have a history of breast cancer. Lamont et al call for further investigation into the mechanisms of this cardioprotective effect.

■ COMMENT BY WILLIAM B. ERSHLER, MD

This is a very interesting observation that may have public health implications. Lamont et al have identified a subset of women who have a 34% reduction in the disease that accounts by far for the largest numbers of deaths in elderly women in the United States. If additional work identifies the mechanism behind this reduction in cardiac risk in breast cancer survivors, the finding may be applicable to the cardiovascular health of the general population.

Three possible explanations come to mind. First, breast cancer survivors by virtue of the rigors of intensive surgical and medical management may be more health conscious and modify those controllable factors relevant to the development of coronary artery disease and acute myocardial infarction (eg, smoking, diet, etc). However, Lamont et al suggest that this explanation is less likely because their data demonstrated that hospitalization rates for other illnesses (eg, pneumonia) were not different in the 2 cohorts. Secondly, estrogens may be etiologic in the development of breast cancer yet protective in atherosclerosis, particularly coronary artery disease. Or, thirdly, a common therapy for breast carcinoma (eg, tamoxifen) may be associated with cardiac protection. Neither the SEER records nor the claims data would allow an accurate estimation of lifetime estrogen exposure or tamoxifen use, and therefore, although quite possibly the case, this association could not be satisfactorily addressed using the resources available. Additional research focused on mechanisms to explain this cardioprotective phenomenon would require data enriched with clinical variables such as tamoxifen use and the influence thereon of certain cardiac risk factors.

Despite the constraints and inherent problems of exploring claims data, the findings that elderly women with a history of postmenopausal breast cancer have a 34% lower hazard of hospitalization for acute myocardial infarction is of great interest. It is quite possible that the cardiac protection relates to the use of SERM's and, therefore, the data may have public health implications for women without a history of breast cancer. Further evaluation to define the mechanisms of this cardioprotective effect is warranted. ■

Isolated Supraclavicular Recurrence of Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: The development of an isolated supraclavicular node recurrence of breast cancer after primary surgical resection (including axillary node dissection) was found, upon review of the tumor registries of 8 community hospitals in The Netherlands, to occur very uncommonly (less than 1%). Examination of clinical outcomes for these patients indicates that isolated supraclavicular recurrence is an antecedent of disseminated disease, in that, even with local control (as achieved by radiation therapy), the great majority of patients soon develop systemic disease.

Source: van der Sangen MC, et al. *Cancer*. 2003;98: 11-17.

The optimal treatment for women who recur with breast cancer in an ipsilateral supraclavicular node without other evidence for distant metastases remains unclear. It is established that women who present with supraclavicular adenopathy develop distant metastases and have a shorter survival than women who present with axillary nodes alone.[1] However, the same cohort—women with supraclavicular nodes at presentation—do fare better than those who present with metastases to distant organs.

In the current report, the experience from 8 community hospitals in the southeastern part of The Netherlands is reported. During an approximate 10-year span, 4669 patients with invasive breast carcinoma underwent axillary lymph node dissection in these hospitals, and follow-up revealed that 42 patients (approximately 1%) developed isolated supraclavicular recurrence without other clinically evident sites of distant metastases. A review of these patients, their therapy, and their clinical course is the subject of this report.

The median interval between treatment of the primary tumor and the diagnosis of supraclavicular recurrence in these 42 patients was 2.5 years (range, 0.2-11.5 years). Radiotherapy was administered to 25 patients (60%), 5 of whom also underwent surgery and 16 of whom also received chemotherapy or hormonal therapy. Eleven patients received hormonal therapy alone, and 4 received chemotherapy alone. One patient received surgical treatment alone, and 1 patient remained untreated. A complete remission was achieved in 35 patients (83%), but a second supraclavicular recurrence occurred

in 12 (34% of patients who achieved complete remission). There were 6 patients (14%) who were alive, without evidence of disease, after a follow-up period of 4.4 to 8.3 years. Nonetheless, the 5-year overall survival and distant disease survival rates based on the date of diagnosis of supraclavicular recurrence were 38% (95% CI, 23%-53%) and 22% (95% CI, 8%-35%), respectively. The distant disease-free survival rate was somewhat better for the 25 patients who underwent radiotherapy as part of the treatment for supraclavicular recurrence than it was for the 17 patients who did not receive radiotherapy (P = .06). When the 8 patients who had received axillary and supraclavicular radiotherapy as part of their initial treatment were excluded, the difference became more dramatic (P = .002). Thus, the experience from this community setting indicates that isolated supraclavicular recurrence occurs uncommonly, but when it does, it is an indicator of soon-to-develop distant metastases. The overall local control rate was quite high with radiotherapy.

■ COMMENT BY WILLIAM B. ERSHLER, MD

It is now established that the appearance of supraclavicular nodes is a poor prognostic factor in breast cancer.[1] A recent report from M.D. Anderson[2] examining the treatment of 70 patients with solitary ipsilateral supraclavicular metastases at first presentation resulted in the argument for developing a treatment strategy specific for this distribution of disease. Brito and colleagues advocated the inclusion of supraclavicular disease in stage III (rather than in stage IV). Ultimately, this recommendation has been followed by the International Union Against Cancer in the most recent edition of the *TNM Classification of Malignant Tumors*.[3] Now, patients with metastases in the supraclavicular lymph nodes are classified as N3c/pN3c and a new stage, stage III C that includes N3 (pN3a, pN3b, pN3c) M0 has been introduced. Previously these malignancies had been classified as M1, and accordingly, Stage IV.

It is logical to think that patients with isolated recurrence in supraclavicular nodes also fall into an intermediate category with regard to prognosis. The data in this report from The Netherlands indicate that local control can be achieved by radiation therapy, but the numbers were too small to demonstrate any survival advantage by additional chemotherapy. Chemotherapy or hormonal therapy alone was less likely to produce local control. Based upon this review, it would seem reasonable that optimal therapy for patients with isolated supraclavicular nodes would include a multimodality approach using local radiotherapy in association with systemic therapy (hormonal or chemotherapy). It remains to be demonstrated that such an approach would result in improved survival (when compared to local therapy alone), but short of a clinical trial established in this particular setting (and unlikely to happen anytime soon), extrapolation from the experience in the adjuvant setting after definitive surgery or radiation therapy would seem reasonable. ■

References

1. DeBois JM. *Strahlenther Onkol.* 1997;173:1-12.
2. Brito RA, et al. *J Clin Oncol*. 2001;19:628-633.
3. Sobin LH, et al, eds. *TNM Classification of Malignant Tumors*, 6th edition. New York, NY: John Wiley & Sons. 2002:131-141.

Radiation Therapy With or Without Extrafascial Hysterectomy for Bulky Stage IB Cervical Carcinoma

ABSTRACT & COMMENTARY

Synopsis: Following radiation therapy, adjuvant extrafascial hysterectomy decreased the risk of relapse for patients with "bulky" stage IB cervical cancer without improving survival.

Source: Keys HM, et al. *Gynecol Oncol*. 2003;89: 343-353.

Keys and colleagues have reported a study of the Gynecologic Oncology Group in which the principal objective was to evaluate, in a randomized trial, the role of adjuvant hysterectomy after standardized radiation in improving progression-free survival and survival for patients with "bulky" stage IB cervical cancer. A total of 256 eligible patients with exophytic or "barrel" shaped tumors measuring > 4 cm were randomized to either external and intracavitary irradiation (RT, n = 124) or attenuated irradiation followed by extrafascial hysterectomy (RT + HYST; n = 132). Tumor size was the most pronounced prognostic factor, followed by performance status 2 and age at diagnosis. Hysterectomy did not increase the frequency of reported grade 3 and 4 adverse effects (both groups, 10%). The majority of these adverse effects were from the gastrointestinal or genitourinary tracts exclusively. There was a lower cumulative incidence of local relapse in the

RT + HYST group (at 5 years, 27% vs 14%). There was no statistical difference in outcomes between regimens except for the adjusted comparison of progression-free survival, although all indicated a lower risk in the adjuvant hysterectomy regimen. Keys et al concluded that, overall, there was no clinically important benefit with the use of extrafascial hysterectomy. However, there is good evidence to suggest that patients with 4-, 5-, and 6-cm tumors may have benefited from extrafascial hysterectomy.

■ COMMENT BY DAVID M. GERSHENSON, MD

Adjuvant hysterectomy after preoperative irradiation rather than irradiation alone in patients with bulky stage IB cervical cancer was first highlighted in a series of reports from M.D. Anderson Cancer Center in the 1960s and 1970s. The rationale of this strategy was based on the premise that tumor hypoxia within a large cervical tumor would be better treated with surgical resection than brachytherapy following external therapy. Of course, the principal objectives of such an approach were to reduce the incidence or local pelvic relapse and to thereby improve overall survival. Following these reports, this treatment approach became widely used throughout the United States without any definitive evidence to support its use. Although the approach was essentially abandoned at M.D. Anderson Cancer Center by the early 1980s, its popularity continued to increase. Amazingly, this GOG trial was conducted between 1984 and 1991, but it was only reported in June 2003. Although Keys et al provide a very positive spin to their conclusions, this study should really signal the death knell for adjuvant extrafascial hysterectomy, except in very specific clinical scenarios. There was only a modest improvement in pelvic control, only a trend toward improvement in progression-free survival, and no improvement in overall survival. Potential indications for adjuvant extrafascial hysterectomy would include patients who have poor anatomy for brachytherapy, those with poor tumor response to irradiation, those with large uterine leiomyomata, and patients in whom there is confusion regarding the primary site of cancer (cervix vs endometrium). The accompanying editorial authored by a well-respected radiation oncologist, Dr. Anthony H. Russell, is very thoughtful and puts this article in the proper perspective.[1] ■

Reference

1. Russell A. *Gynecol Oncol*. 2003;89:341-342.

Dr. Gershenson is Professor and Chairman, Department of Gynecology, M.D. Anderson Cancer Center, Houston, Tex.

CME Questions

5. Which of the following statements about the isolated recurrence of breast cancer in an ipsilateral supraclavicular node is *not* true?

a. Treatment with radiotherapy is likely to achieve local control.
b. Treatment with chemotherapy enhances survival time.
c. Metastatic disease at other sites is likely to become apparent within 1-2 years.
d. Chemotherapy and/or hormonal therapy are typically inadequate to achieve local control.

6. Which of the following statements about the development of acute myocardial infarction in women with a history of breast cancer has been satisfactorily established?

a. The rate of acute myocardial infarction is less in women previously treated for breast cancer metastatic to bone.
b. The rate of acute myocardial infarction is less in women with a history of stage I or II breast cancer.
c. The use of tamoxifen has been shown to reduce the incidence of acute myocardial infarction in women with breast carcinoma.
d. All of the above

7. Regarding the ICON4/AGO-OVAR-2.2 trial for relapsed ovarian cancer in women with a disease-free interval of 6 months or more, which of the following statements is true?

a. Women who received paclitaxel as initial therapy were not likely to benefit from a platinum-paclitaxel combination.
b. Women who received carboplatin as initial therapy were not likely to benefit from a carboplatin-paclitaxel combination.
c. Women who received cyclophosphamide in combination with carboplatin as initial therapy were not likely to benefit from a carboplatin-paclitaxel combination.
d. Women who received paclitaxel and carboplatin in combination for the relapsed disease were more likely to achieve benefit from treatment than those who received carboplatin alone.

Answers: 5 (b); 6 (b); 7 (d)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Oncology Alert*. Send your questions to: Robert Kimball, Clinical Oncology Alert, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Oncology Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. ■

Attention Readers . . .

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

In Future Issues:

One Pill to Prevent Hair Loss and Prostate Cancer